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Change in obesity-related metabolic abnormalities associated with BMI improvement through life-style intervention: a meta-regression.

Running Title:

Changes in obesity-related metabolic abnormalities with BMI change: a meta-regression

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Abstract (249 wds)

Objective

The reduction in body mass index standard deviation score (BMI-SDS) associated with improvement in biomarkers relating to metabolic health in obese children is unknown. We aimed to establish the change in BMI-SDS associated with improved inflammation, liver function and insulin resistance to inform clinical guidelines for paediatric weight management interventions and to assess the efficacy of future trials.

Methods

A large-scale systematic review was conducted to identify relevant studies. Studies of children with a diagnosis of obesity according to defined BMI thresholds, participating in lifestyle interventions to reduce obesity, were included. Studies must have reported baseline (pre-) and post-intervention (or change of) BMI-SDS and either fasting glucose, homeostatic model of insulin resistance (HOMA-IR), alanine aminotransferase (ALT), C-reactive protein (CRP), or interleukin-6 (IL-6). A series of meta-regressions were conducted to establish links between BMI-SDS change scores and change in metabolic markers of health.

Results

Sixty-eight papers were identified. From the meta-regression analyses, across all study subsets, greater mean falls in all four parameters, (HOMA-IR, Glucose, ALT and CRP) were observed with greater mean loss of BMI-SDS, but the trends were only statistically significant for HOMA-IR and CRP (P=0.003; P=0.021). However, we could not find minimum changes in BMI-SDS that would ensure a fall in these outcomes.

Conclusion

At this time, we are unable to recommend a definitive value of BMI-SDS reduction needed to improve the markers of metabolic health. Future trials should aim to report additional indices of derived BMI values which may better reflect changes in actual adiposity.

Key words: Obesity, Insulin resistance, meta-regression, BMI-SDS, metabolic health.

Abbreviations:

T2DM: Type 2 Diabetes Mellitus

BMI-SDS: body mass index- standard deviation score

RCT: randomised controlled trial

IOTF: International Obesity Task Force

HOMA: Homeostatic model assessment

IL6: Interleukin 6

ALT: Alanine Aminotransferase

CRP: C-reactive Protein

HTA: Health Technology Assessment

SD: standard deviation

SE: standard error

CI: Confidence interval

PI: Prediction interval

IQR: Interquartile range

Introduction

There has been a ten-fold increase in the number of obese children worldwide since 1975[1]. Childhood obesity is associated with a range of health problems both in childhood and later life[2]. Conditions once limited to adult populations, such as type 2 diabetes (T2DM) and fatty liver disease, are now being documented in children[3]. Not only is avoidable, sub-optimal health a concern for the obese individual, but the financial burden and stress that increasing obesity levels place on health services must not be overlooked[4]. Effective weight management programmes to tackle childhood obesity are therefore of importance.

Weight-loss targets that can produce clinically useful reductions in risk have been established for obese adults[5]. Setting defined targets in children is more difficult as a result of the influence of growth. A standardised body mass index score (BMI-SDS) is used to assess weight status in children as they grow[6], providing a normalised measure for the degree of obesity. The reduction in BMI-SDS needed to effect clinically significant reductions in risk of metabolic factors is currently unknown.

Insulin resistance

Being overweight or obese may cause insulin resistance[7]. Evidence has shown that insulin resistance and glucose tolerance may improve through exercise and/or dietary modification[8]. Ford *et al*[9] demonstrated that a reduction of BMI-SDS ≥ 0.25 improved insulin resistance, with further benefit accrued if BMI-SDS was reduced by ≥ 0.5. Reinehr *et al*[10] also investigated change in insulin sensitivity with regards to change in BMI-SDS. There was no change in insulin sensitivity for groups with small (BMI-SDS reduction of <0.25) or moderate (BMI-SDS reduction of ≥ 0.25 or <0.5) weight-loss. In the group that achieved large amounts of weight-loss (BMI-SDS reduction of ≥ 0.5), insulin sensitivity improved.

Inflammation

Insulin resistance and poor blood glucose regulation are interlinked with low-grade chronic inflammation as a result of increased adipose tissue[11]. Interleukin-6 (IL-6) and C-reactive protein (CRP) are two commonly reported inflammatory markers that are modified by increasing adiposity. IL-6 and CRP have both been linked with increased insulin resistance and also contribute to atherosclerotic plaque development in adults[12].IL-6 has been linked to detrimental health outcomes in obese children, such as endothelial dysfunction [13]. A systematic review by Sirico *et al*[14] in 2018 reviewed the effect of physical exercise interventions (n = 7) on inflammatory markers in childhood obesity, and found reductions in both IL-6 and CRP. There is insufficient long-term data linking CRP levels in childhood directly to disease outcomes in adulthood, but early identification of such markers and management with appropriate interventions may reduce the risk of future disease[15].

Liver function

Non-alcoholic fatty liver disease (NAFLD) is a complication of increasing adiposity, where fatty deposits develop within the liver. NAFLD is characterised by increasing levels of intrahepatic triglyceride content, with or without inflammation and fibrosis[16]. A review by Anderson et al 2015 found that the prevalence of NAFLD in childhood obesity clinics was 34.2%, in comparison to 7.6% in children in general population studies[17]. Raised levels of the hepatic enzyme Alanine Aminotransferase (ALT) indicate liver damage and can be used as a marker for fatty liver disease[18].

Chronic inflammation as a result of obesity may cause hepatic insulin resistance, contributing further to overall insulin resistance, disordered glucose metabolism and metabolic syndrome, but the relationship between NAFLD and insulin resistance may be bi-directional[19]. Utz-Melere *et al*[201]

undertook a review on the impact of lifestyle changes on BMI, aminotransferases and steatosis in children and adolescents with NAFLD (n=19 studies). They found the majority of the studies reported beneficial changes in ALT levels, reporting a combined effect. Using a random effects model, the standardised mean difference (SMD) was -1.35 but the confidence interval was wide (95% CI -1.92 to -0.78) as a result of heterogeneity in the studies. Further, Utz-Melere *et al* found that lifestyle improvements had a significant impact on steatosis, reducing risk by 61%. These changes were reported as a result of lifestyle change, even in the absence of significant weight reduction.

Summary

This paper is part of a series of reports from a large-scale systematic review completed in early 2018 (PROSPERO CRD42016025317). The aim of the review was to establish the changes in BMI-SDS necessary to effect improvements in metabolic health in obese children and adolescents. In total, 90 studies were included (searched up to May 2017). The first paper focussed on the link between BMI-SDS and measures of adiposity (using body fat %) (Birch et al.[21]) and another paper focusses on the link between BMI-SDS and cardiovascular outcomes.

Objective

We aimed to establish the minimum change in BMI-SDS associated with improvements in relation to blood glucose regulation, inflammation, insulin sensitivity/resistance, and liver function in obese children and adolescents.

Methods

The methods used to conduct the systematic review have been reported in detail in a previous publication (Birch et al[21]). Studies were identified by searching five electronic databases from inception to May 2017. A summary of the systematic review's inclusion criteria and data extraction process can be found in Appendix 1. Specifically, this paper focuses on the following data extracted from the included studies: fasting glucose, Homeostatic Model Assessment of insulin resistance (HOMA-IR), IL-6, CRP, and ALT.

Quality assessment

Two members of the review team assessed the quality of the included papers using the Quality Assessment tool used in the 2004 Health Technology Assessment (HTA) systematic review of the long term effects and economic consequences of treatments for obesity and implications for health improvement[22] (see Birch et al[21] and Supplement 1 for further details).

Deviations from protocol

In the protocol for this systematic review (PROSPERO CRD42016025317) it was stipulated that no case-control studies were to be included. We allowed the inclusion of one study described as case-control[33], but on closer inspection, this was actually a cohort study.

Analysis

We used random-effects meta-regression as implemented in Stata[23] to separately quantify the relationship between the mean changes in BMI-SDS/z-score (independent, predictor variable) and mean changes in: (i) HOMA-IR, (ii) fasting glucose, (iii)ALT, (iv) CRP and (v) IL-6 (target variable), where the latter, target variables were either reported directly, or were able to be calculated from reported data. In each case, we were not trying to assess the relative effects of the various

interventions, but rather to examine the relationships between the two sets of outcomes; meta-regression allows for residual heterogeneity in the target variable not explained by the predictor. Essentially our approach was the same as that adopted in our first paper. Subgroups reported within the same study, however subdivided (i.e. intervention vs control, boys vs girls or good responders vs poor responders), were regarded as independent observations and used in preference to aggregated results from the whole study if both were reported. Standard deviations (SDs) were calculated from Standard Errors (SEs) or 95% confidence intervals (CIs) for the mean. If medians and ranges/interquartile ranges (IQRs) were reported rather than means/SDs, the latter were estimated from the former[24]; in one study[25] which reported geometric mean and range for some target variables, the geometric means were used as a proxy for the medians. Analysis required the means/SDs of the *changes* in the target variables; where studies reported only pre- (baseline) and post- (intervention or control) values, values for the changes were estimated. SDs for the latter required a knowledge of the correlation coefficient between baseline and post-intervention results; we estimated these from studies reporting both sets of results and used their median. In our first paper[21] we carried out sensitivity analyses using different values of R, the results were little changed.

The fitted regression lines are plotted together with their 95% prediction intervals (PIs); individual points represent individual study subgroup results (the mean change in the target variable and the mean change in BMI-SDS) with the size of the surrounding circles representing the precision of the mean change in the target variable (i.e. the reciprocal of the SE squared). For a given mean change in BMI-SDS, the upper and lower limits of the 95% PI indicate the range of mean changes in target values that would be expected in future studies.

Results

Ninety-eight published articles from 90 different studies met the inclusion criteria for the entire systematic review. The flow diagram (Fig. 1) illustrates the number of papers excluded at each stage of the review. Further information regarding the search results can be found in Supplement S1.

Figure 1: Flow diagram of the systematic review that identified the included studies

INSERT FIGURE 1 HERE

Outcome measures

In total, 68 studies reported metabolic measures and details of these are listed in Table 1[26-100], alongside the outcome(s) of interest from each study. Whilst various glucose measures were reported, we focused on fasting-glucose measurements for this paper (56 studies), as fasting glucose is used clinically to identify pre-diabetes and diabetes. Although several insulin measures were reported, we focussed on HOMA-IR (66 studies) as a simple and routinely measured estimate of insulin resistance. The inflammation measures reported here are CRP (21 studies) and IL-6 (6 studies). Finally, the measure of liver function reported here is ALT (21 studies).

Narrative description of studies included in this paper

Of these 68 studies, 47 were conducted in Europe, 15 in the Americas and six elsewhere in the world. Most studies defined obesity as a BMI-SDS>2 or a BMI percentile of at least the 90th percentile. Most of the studies were of cohort design (n = 49) and 16 were randomised controlled trials (RCTs). There was one study that adopted a quasi-randomised design[30], one that was case-control[39] and another that was a non-randomised prospective study[73],

Most interventions were conducted in hospital clinic settings (n=56). Six studies were interventions in the community and four in academic institutions. One group conducted their intervention between community and hospital clinic setting[91,92], and one conducted their intervention between the community and academic institution[37].

Fifty-six studies conducted interventions that comprised both diet and exercise components. The remaining studies (n=12) utilised interventions that focused either on exercise or diet only.

Duration of the interventions ranged from 2 to 24 months, with one study having no specific intervention period[42]. The majority of studies (n=59) did not report any follow-up after the lifestyle treatment intervention. The duration of follow-up in the studies where it was conducted and reported, ranged from 6 to 24 months.

The sample sizes of the included studies ranged from 8 to 1017 participants. The age of the participants ranged from 4 to 19 years. Studies predominantly had a mix of males and females with only three studies specifically focused on either only girls[61,62] or boys[83]. Forty studies (59%) measured the pubertal development stage of participants according to the Marshall and Tanner staging[101], with pubertal status categorised into three groups: prepubertal, pubertal, and late/post-pubertal. One study reported that pubertal development was measured but the method used was not defined[37], and one study reported the percentage of prepubertal participants without defining how they measured puberty[95]. Twenty-six studies (38%) did not report any measures of pubertal development.

Table 1: Characteristics of studies reporting adiposity outcomes

(INSERT TABLE 1 HERE)

Quantitative analysis

HOMA-IR

Fifty-eight distinct studies had available data on HOMA-IR, with one omitted from analysis[85] (as CIs derived from logarithmically transformed data made it impossible to ascertain SDs for HOMA-IR). The 57 studies yielded 105 useable data subsets after exclusion of one subset with incomplete data[51]. Means/SDs of the *changes* in HOMA-IR, however, were only available in 22 of the 105. Fourteen of these also had pre- and post- mean/SDs and the median of the correlation coefficients (r) estimated for these was 0.66 (IQR: 0.25-0.75). This value was used to estimate the SD of the changes for each of the remaining 83 subsets.

Figure 2 shows the results of the meta-regression of the relationship between mean change in HOMA-IR and the mean change in BMI-SDS across the 105 data sub-sets. The fitted regression line here is: **Mean fall in HOMA-IR = 0.683 x Mean change in BMI-SDS -0.171.** The slope was statistically significant (0.683, 95%CI 0.243-1.122, P=0.003), confirming a relationship between the variables across the study subsets, however from the prediction intervals it was not possible to determine a mean reduction of BMI-SDS that would 'ensure' a fall in mean HOMA-IR in a future study since the upper limit of the 95% prediction interval was never wholly below 0.

Figure 2: Meta-regression of relationship between mean change in HOMA-IR and the mean change in BMI-SDS (n=105 subsets).

INSERT FIG 2 HERE

The standardized predicted random effects were approximately normal (see Appendix 1 Figure A(i)). A further analysis excluding two possible outliers (with mean change in HOMA-IR>2)

produced very similar results (results not shown). In separate analyses, the %females were added to the regression model. The %females was not statistically significant (P=0.30).

Appendix 2 also contains further analyses. Figure A(ii) highlights (in red) the four study subsets where geometric means were used interchangeable with medians (see Analysis section above). These four results seemed consistent with the remainder and their exclusion did not change our overall findings. Figure A(iii) shows the analysis of the 22 subsets where the mean/SD of the changes in HOMA-IR were obtained directly from the research documentation (thus avoiding using an estimate of r).

Fasting Glucose

There were 52 distinct fasting glucose studies, with one omitted from analysis[58] as it was not possible to ascertain glucose SDs. The remaining 51 studies yielded data on 93 subsets; but one was unusable[65] (one subset too small to estimate glucose SD from IQR). Only eight of the remaining 92 study subsets provided mean/SD of the *changes* in glucose values. Across these there was no significant relationship with mean change in BMI-SDS (data not shown), but the number of studies was small and spanned only a narrow range of BMI-SDS changes. The median of the correlation coefficients estimated from three subsets that provided SDs for the pre-, post- and change in glucose measurements was 0.69 (range 0.53-0.92). Using this, the SDs of the changes in glucose were estimated for the remaining 84 subsets.

The resulting meta-regression on the full data set (n=92) is shown in Figure 3 below. The meta-regression line fitted was: **Mean fall in Glucose = 0.069 x Mean change in BMI-SDS -0.008.** There was a small positive slope which was not statistically significant (0.069, 95%CI -0.025 to 0.163, P=0.15). From the prediction intervals, it was not possible to determine a mean reduction in BMI-SDS that would ensure a fall in fasting glucose.

Figure 3: Meta-regression of relationship between mean change in fasting glucose and the mean change in BMI-SDS (n=92 subsets)

INSERT FIGURE 3 HERE

A half normal plot for the standardized predicted random effects, shown in Figure B(i) of Appendix 2, suggested two possible outliers, each from different studies but both with mean change in fasting glucose<-0.5 in Figure 3 above. Exclusion of these two outliers did not change the overall findings (Appendix 2 Figure B(ii)).

When added to the meta-regression, the %females in the subset did not significantly affect the change in glucose (P=0.89)

ALT

Twenty studies provided data on ALT, with two omitted from analysis[85,89] (one used geometric means for BMI-SDS and there was uncertainty with the other whether range or IQR for ALT was reported). The remaining 18 studies yielded 28 subsets for analysis. Only four subsets provided mean/SD of the changes in ALT, too few for separate analysis. Two of these provided SDs for each of the pre-, post and changes in ALT; correlation coefficients estimated from the latter were 0.97 and 0.88; their mean/median value of 0.93 was used to estimate the SD of the changes in ALT for the remaining 24 subsets.

The meta-regression on the full data set (n=28) is shown in Figure 4.

The meta-regression line fitted was: **Mean fall in ALT = 4.00 x Mean change in BMI-SDS – 3.90.** The slope was positive but not statistically significant (4.00 95%CI -3.03 to 11.02; P=0.253). From the prediction interval it was not possible to determine a mean reduction in

BMI-SDS to ensure a mean fall in ALT. A half normal plot for the standardized predicted random effects, is shown in Figure C(i), Appendix 2.

Figure 4: Meta-regression of relationship between mean change in ALT and the mean change in BMI-SDS (n=28 subsets)

INSERT FIGURE 4 HERE

What added to the meta-regression the %females were significant determinants of the change in ALT (p=0.80).

A further analysis which excluded a potential outlier subset (with change in ALT<20 in Figure 5 above) did not change the results.

CRP

Nineteen studies provided data on CRP with one omitted from analysis[60] (as it presented logged values) yielded 36 data subsets for analysis. Only three subsets yielded mean/SDs for the change in CRP but all 3 had pre- and post- SDS as well and therefore could be used to estimate correlation coefficients. The median of these was 0.69 (range 0.58-0.80) which was used to estimate the SD of the changes in the remaining 33 studies. The meta-regression for the full data set (n=36) is shown in Figure 5.

The regression line was **Mean fall in CRP = 0.48 x Mean change in BMI-SDS + 0.03,**

The positive slope was statistically significant (0.48, 95%CI 0.08-0.89; P=0.021) although from the PIs it was not possible to determine a change in mean BMI-SDS that would ensure a fall in CRP. A half normal plot for the standardized predicted random effects, is shown in Figure D(i) of Appendix 2.

Figure 5: Meta-regression of relationship between mean change in CRP and the mean change in BMI-SDS (n=36 subsets)

INSERT FIGURE 5 HERE

As was the case with HOMA-IR, the CRP data in Ford *et al* 2010(b) had been expressed as geometric means and used here as proxys for medians; analysis excluding these four subsets however did not change the findings. When added to the meta-regression model, neither %females related to the change in CRP (P=0.48).

IL-6

As only six studies reported IL-6, we deemed it appropriate to report just a narrative description of the data (represented as mean (SD)). The mean baseline BMI-SDS was 3.51(1.04), the mean end of intervention BMI-SDS was 2.97 (0.76) and the mean change from baseline to the end of intervention was -0.54 (0.49). The mean baseline levels of IL-6 were 2.04 pg/ml (0.58), and the mean end of intervention levels of IL-6 were 2.11 pg/ml (0.88), which gave a mean change of IL-6 of 0.07 pg/ml (0.52).

DISCUSSION

Summary of main results

The objective of this paper was to attempt to establish the minimum change in BMI-SDS needed to achieve improvements in metabolic health in this population. Sixty-eight papers reported on the parameters of interest in this paper (HOMA-IR, fasting glucose, ALT, CRP).

From the meta-regression analyses, across all study subsets, greater mean falls in all four parameters (HOMA-IR, fasting glucose, ALT and CRP) were observed with greater reduction of BMI-SDS, although the trends were only statistically significant for HOMA-IR and CRP (P=0.003; P=0.021). Looking specifically at the prediction intervals, however, we could not find minimum changes in mean BMI-SDS that would ensure a fall in these outcomes. Our model hinted that a greater change in mean glucose might be obtainable for the same change in mean BMI-SDS achieved over a longer duration, but further evaluation was difficult.

Strengths and limitations

We believe that this is the first paper to attempt to bring together all studies that have reported both a change in BMI-SDS and changes in markers of metabolic health, including liver function, in the obese paediatric population. In some cases, there were variations in reporting of results where multiple publications reported on the same study; where this occurred the results from the most comprehensive paper were used (See Supplementary material S1). Consideration to the strengths and limitations of the full systematic review conducted have been discussed in Birch *et al*[21].

Agreements and disagreements with other research

Whilst there has been previous evaluation of the effects of lifestyle interventions for treating overweight and obesity in children and adolescents [103,104,105], the main focus of these reviews has

been the change in BMI and BMI z-score achieved, and few have examined the effects on metabolic risk. Our findings regarding improved CRP with BMI-SDS reduction are in line with the findings from a systematic review by Sirico et al[14], who reviewed the effect of physical exercise interventions on inflammatory markers in childhood obesity reporting CRP reductions alongside IL-6. Our analyses also identified a statistically significant reduction in insulin resistance (measured as HOMA-IR) associated with BMI-SDS reduction. A systematic review and meta-analysis conducted by Ho et al[106] of the effects of lifestyle interventions on cardio-metabolic outcomes in overweight and obese children, identified 15 studies which reported fasting insulin. The results of their meta-analysis indicated that lifestyle interventions produced significant weight-loss compared with no-treatment control conditions (BMI: -1.25kg/m2, 95% CI -2.18 to 0.32; BMI z-score: -0.10, 95% CI -0.18 to -0.02) and led to significant improvements in fasting insulin (-55.1pmol/L, 95% CI -71.2 to -39.1).

Clinical implications

The findings from our meta-regressions indicate that a reduction in BMI-SDS is associated with improvements in insulin resistance (HOMA-IR) and inflammation (CRP). However, from these analyses, we are currently unable to set any specific parameters for the required change in BMI-SDS needed to affect positive clinical outcomes. More evidence is needed before such parameters can be identified and used in a clinical setting.

Recommendations for future research

Given the apparent lack of evidence that changes in BMI-SDS accurately reflect changes in metabolic health with childhood obesity, it seems prudent for future trials to report additional indices of derived BMI values which may better reflect changes in actual adiposity. In addition, if the studies included were of longer duration, a greater improvement in some of these markers (particularly fasting glucose) may have been possible.

Conclusion

At this time, based on the findings of this review, we are unable to recommend a definitive value of BMI-SDS reduction needed to improve the markers of metabolic health (Fasting glucose, ALT, IL-6). Despite significant trends in reduction of BMI-SDS in relation to both HOMA-IR and CRP, we were unable to identify minimum changes in BMI-SDS that would ensure a fall in these outcomes. Future trials should aim to report additional indices of derived BMI values which may better reflect changes in actual adiposity.

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Table 1: Characteristics of studies with outcomes reported

	Author, Year, Country (Intervention name)	Study design: Sample size (n)	Obesity definition	Age range (inclusion): Mean ± (SD) Sex (% F)	Pubertal status measured	Diet D)/ Exercise (E)/D+E: Setting	Format & content	Duration (months): Follow up (months)	Outcomes reported
1	Aeberli, 2010[26] & Murer 2011[27], Switzerland	Cohort: Total: 203	BMI > 98th %ile	Aeberli: Age range:10-18: 14.1 ± 1.9 F=42% Murer: Age range: NR 14.1 ± 2.0 F=44%	NR	D+E: Clinic/ hospital	Moderate caloric restriction.2 x 60-90min/day endurance exercise + 4-5 hr/wk. exercise session + behaviour modification.	2: 0	HOMA-IR, and fasting glucose.
2	Bell 2007[28], Australia	Cohort: Total = 14	BMI >95th %ile	Age range: 9-16: 12.7 ± 2.32 F= 43%	Yes- Tanner	E (Community)	8 weeks structured circuits exercise training: 3 x 1hr sessions/week. No standard dietary modifications.	8: 0	Fasting glucose and ALT
3	Bock 2014[29] Canada HIP KIDS	Cohort: Total = 42	BMI ≥ 95th %ile (CDC)	Age range: 8-17 12.8 ± 3.14 F=50%	Yes - Tanner	D+E: Clinic (Hospital)	Intensive phase (3 mths): bi-wkly 90 min counselling. Maintenance phase (9 months): alternating mthly gp or individual sessions (90 mins). Sessions focus on exercise/psychosocial/behavioural aspects.	12: 0	HOMA-IR, fasting glucose, and ALT
4	Bruyndonckz 2015[30], Belgium	Quasi-randomised trial: Total = 61 I = 33 C = 28	BMI ≥ 97th %ile adolescents <16 yrs; BMI ≥ 35 adolescents ≥ 16 yrs	Age range: 12-18 iI: 15.4 ± 1.5 C: 15.1 ± 1.2 F=75%	NR	D+E: Clinic (Hospital)	Intervention: Dietary restriction 1500-1800 kcal/day + 2 hrs/day supervised play/lifestyle activities + 2hrs/wk PE + 3 x 40min/wk supervised training session. Control: Usual care.	10: 0	HOMA-IR and CRP
5	Bustos 2015[31] Chile	Cohort: Total = 50 (28 completed)	CDC	Age range: NR 9.5 ± 1.9 F=47.6%	NR	D+E: Academic Institution	Nutrition/behavioural modification session 40 min/wk + PA 50 min x2/wk+ Family support every 15 days for first 2 mnths, then mthly.	8: 0	HOMA-IR, fasting glucose, and ALT
6	Calcaterra 2013[32] Italy	Cohort: Total = 22	BMI > 95th %ile	Age range: 9-16 13.23 ± 1.76 F=41%	Yes - Tanner	E: academic institution	2 x 90 mins exercise training sessions/wk	3: 0	HOMA-IR, and fasting glucose.
7	Corripio 2010[33] Spain	Case-Control: Total=72 (62 completed)	BMI> 2SDS. Spanish Normative charts.	Age range: 6-10. 8.03 ±1.08. F=51%	Yes-Tanner	D+E: Clinic (Hospital)	Balanced normocalorie diet (30% fat + 15% protein + 55% CHO) + Limited 2hr/day tv/video games + 3 x 30-40 min moderate exercise/wk.	24: 0	HOMA-IR, and fasting glucose.
8	Dobe 2011[34] Germany OBELDICKS – mini	Cohort: Total = 103 (Obeldicks - Mini)	>97th to 99.5th %ile	Age range: 4-8 yrs 6.1 +/- 1 F=56%	NR	D+E: Academic Institution	Obeldicks	12: 0	HOMA-IR and fasting glucose.

9	Farpour-Lambert 2009[35] Switzerland.	RCT: Total = 44 I = 22, Obese C =22	BMI > 97th %ile	Age range: 6-11. 8.9 ± 1.5 F=64%	Yes- Tanner	E Clinic (Hospital)	180 min/wk PA + 135 min/wk PE	3: 0	HOMA-IR, fasting glucose, and CRP
10	Ford, 2010 A+B[9,36] UK	RCT: Total = 106	BMI ≥ 95th %ile (CDC)	Mandometer: 9.0 - 16.9 SC: 9.1 - 17.5 Mandometer: 12.7 ± 2.2 SC: 12.5 ± 2.3 F=56%	Yes- Tanner	D Clinic (Hospital)	Mandometer device to regulate rate of eating and total intake vs SC	12: 0	HOMA-IR and CRP.
11	Gajewska, 2016[37] Poland.	Cohort: Total = 100	BMI SDS > 2	Age range: 5-10. 8.1 (6.8-9.2) with weight loss. 8,8 (7,3-9.6) without weight-loss. F=53%	Reported with tanner stage, any with pubertal development excluded.	D+E: Community and Academic institution	3-mth intervention, low energy diet (1200-1400kcal), 3-5 meals every day, instructions concerning PA, 10-14 food day diary, 3-day food diary.	3: 0	Fasting glucose.
12	Garanty-Bogacka [38], 2011 Poland.	Cohort: Total = 50	BMI > 97th %ile (ref data for Polish children)	Age range: 8-18 14.2 ± 2.6 F=58%	Yes- Tanner	D+E: Clinic (Hospital)	Exercise therapy (Instructions in PA + reducing sedentary behaviour) + Reduction in fat and sugar intake.	6: 0	HOMA-IR, fasting glucose, CRP, and IL-6.
13	Gronbaek 2012[39] & Kazankov 2014 [40] Denmark Julemaerkehjemmet Hobro	Cohort: Total = 117 (71 completers)	ND. Obese. Baseline BMI-SDS: 2.93±0.52	Age range: NR 12.1 ± 1.3 F=56%	NR	D+E: Community	Individually designed healthy diet + moderately strenuous PA program (at least 1hr/day).	2.5 months/10 weeks: 12	HOMA-IR, fasting glucose, CRP and ALT.
14	Grulich-Henn 2011[41], Germany	Cohort: Total = 58.	BMI>97th %ile (German paed. Standard). F=55%.	Age range: 8-17. (median) 12.6. F=58%	NR	D+E: Clinic (Hospital)	6 x monthly nutritional consultation & cognitive behavioural training + 24 weekly PA programs.	6: 0	HOMA-IR, and fasting glucose.
15	Gunnarsdottir 2014[42] Iceland	Cohort: Total=110	BMI z-score > 2.0 SDS (Swedish growth curve)	Age range: 8-13. 10.6 ± 1.4. F=45%	NR	D+E Clinic (hospital)	Family-based Epstein behavioural intervention.	3: 0	ALT
16	Huang 2010[43] Mexico	Cohort: Total=85 (61 completers)	BMI > 95th %ile (CDC)	Age range: 10-16. 11.9 ± 1.4 F=42.6%	Yes- Tanner	D+E Clinic (Hospital)	Parents (4 sessions/wk lifestyle support in 1st month + 15 min/month telephone session) + Children (Low calorie diet + 30 min/day brisk walk for 1st 2 wks, then 1 hr by 3rd wk + Moderate intensity exercise 5 times/wk encouraged).	6: 0	HOMA-IR, and fasting glucose
17	Huang 2014[44] Mexico	Cohort: Total=70 (54 completers)	BMI > 95th %ile (CDC)	Age range: 10-16. 13.6 ± 1.3. F=41%	Yes- Tanner	D+E. Clinic (Hospital)	Parents (4 sessions/wk lifestyle support in 1st month + 15 min/month telephone session) + Children (Low calorie diet + 30 min/day brisk walk for 1st 2 wks, then 1 hr by 3rd wk + Moderate intensity exercise 5 times/wk encouraged).	6: 0	HOMA-IR, and fasting glucose
18	Kalavainen, 2012[45] Finland	RCT: Total=70	Wt-for-ht 115-182%	Age range: 6.6-9.7. 8.1±0.8 F=60%	Yes- Tanner	D+E. Community	2 interventions (Group and routine) - Routine (2 school heath care sessions) + Group (10 x 90 min/wk parents and children separate focusing on	6: 6	HOMA-IR, and fasting glucose

							healthy lifestyle/physical activity session, then next 5 sessions/2 wks + 1 session together) 6		
19	Koot 2016[46] Netherlands	Cohort: Total=51 (44 completed)	BMI-for-age > 35 kgm² OR BMI-for-age > 30 kgm² + obesity related comorbidities. Baseline BMI-SDS: 3.5±0.5	Age range: 8-18. Inpt tx: 14.9 ± 2.5 Ambulatory tx: 14.4 ± 2.1 Usual care: 14.7 ± 2.4. Inpt tx F=56% Ambulatory tx F=24% Usual care F=50%	Yes -Tanner	D+E. Clinic (Hospital).	Long inpt (6 months tx on working days + follow-up of 6 monthly return visits of 2 days); Short inpt (2 months tx on working days + 4 months biweekly return visits of 2 days + follow-up 6 monthly return visits of 2 days); Ambulatory setting (16 days ambulatory visits at increasing time-intervals over 6 month period + follow-up ambulatory visits 6 wks, and 3, 6, 9, 12 months after end of treatment); Home-based usual care (6 month continuation of care in local setting). Interventions focused on nutrition/behavioural sessions, increasing physical activity, and decreasing sedentary behaviour	6 months treatment on working days + follow-up of 6 monthly return visits of 2 day	HOMA-IR
20	Mager 2015[47], Canada	Cohort Total=12 (completed =9)	CDC and prevention criteria	Age range: 7 to 18. 13.6±2.6. F=8%	NR	D: Clinic	Low glycemic index, glycaemic load and fructose diet. 1 session of education for parents and children, then monthly follow up calls to review dietary principles.	6: 0	HOMA-IR, fasting glucose, CRP, IL-6, and ALT.
21	Makkes 2016[48], The Netherlands.	RCT: Total = 80. Short-stay (SS)=40 Long-stay (LS)=40	99th and comorbidity and 99.9th 4th Dutch national growth study of 1997. SDS-BMI equal to or over 3.0 or SDS-bmi equal to or over 2.3 + obesity related comorbidity	Age range: 8-19 Total: 14.8 +/- 2.3 SS (2 mths): 14.5 +/- 2.4. LS (6 mths): 15+/- 2.2 Total F=66% SS F= 70% LS F =63%	NR	D+E: Clinic (Hospital)	Treatment: Focused on nutrition, physical activity and behaviour change and required active participation of parent/caregiver.	1 year, with 1 year follow up after.	HOMA-IR, and fasting glucose.
22	Marcano 2011[49] Venezuela	Cohort: Total=111.	Ob: BMI>97th %ile/BMI z-score >2	Age range: NR. 11.3±2.8 F=57%	Yes- Tanner	D+E: Clinic (Hospital)	Nutrition + PA recommendations + A form to register weekly hours of physical activity, number of steps taken/day, and hrs/wk spent in sedentary activities + Restrict calorie intake and focus on a balanced diet encouraged.	8: 0	HOMA-IR, fasting glucose, and CRP.
23	Martos 2009[50] Spain	Cohort: Total = 47	BMI > 95th %ile in growth curves	Age range: 6-9. 8.0±0.15. F=60%	Yes- Tanner.	D+E: Community	Moderately ob subjects (Low-calorie diet); Severe/refractory ob subjects (Restriction diet of 25-30%) + Moderate/intense exercise 60 min/day x 5 days/wk encouraged	9: 0	HOMA-IR, fasting glucose, CRP and IL-6.
24	Meyer 2006[51] Germany	RCT: Total = 67 (I = =33 Obese C=34)	BMI > 97th %ile (German paediatric population)	Age range: 11-16 I: 13.7 ± 2.1 Ob C: 14.1 ± 2.4 F=48%	Yes - Tanner	E: Clinic (Hospital)	3 x exercise sessions (Monday: swimming and aqua aerobic training 60 min + Wednesday sports games 90 min + Friday walking 60 min)/ wk; Control: Maintain current level of PA	6: 0	HOMA-IR, and CRP
25	Miraglia 2015[52] Brazil	Cohort: Total = 27	BMI z-score > 2	Age range: 6-13 Median 10.3 F=48%	NR	D+E: Clinic (Hospital)	AmO: Outpatient Ambulatory. Obesity outpatient clinic - lifestyle change based on goals agreed relative to feeding habits & physical exercise, followed mthly. 12 mths: Subjects	12: 0	HOMA-IR.

							assessed at inclusion & after 12 mths of FU to obtain anthropometric & adipokine measurements.		
26	Montero 2014[53], Spain	Cohort: Total=17	>3 BMI z-scre. International obesity task force.	Age range: NR. 13.45 ± 1.18. F=70%.	Yes- Tanner	D+E: Clinic (Weight management centre)	Moderately hypocaloric diet (reduction of between 300-500kcals) while performing physical activity programme of 4x90 minutes supervised sessions per week	16: 0	CRP.
27	Morell-Azanza 2017[54] & Rendo-Urteaga 2015[55] Spain	Cohort: Total = 40	OW/Ob as per Cole et al 2000 criteria	Age range: 7-15 yrs 11 F=53%	Yes – Tanner	D: Clinic (Hospital)	Moderate energy-restricted diet + nutritional education + family involvement.	2.5: 0	HOMA-IR, fasting glucose, CRP and IL-6.
29	Murdolo 2017[56] Italy	Cohort: Total = 53	NR	Age range: 5-13. Responders: 9.0 ± 1.1 F=50% Non-responders: 2.09 ± 0.32 F=33%	Yes -Tanner	D+E: Community	Educational Wt Excess Reduction Program	24: >6 months	HOMA-IR
29	Obert 2013[57], France	Cohort: Total = 28	BMI>97th %ile	Age range: NR. 14.2±1.5. F=47%.	NR	D+E: Clinic (Hospital)	Cycle ergometer (9 x 5 mins x 3 times/week: 4 min moderate + 1 min intense) + 2 times/wk moderate exercise for 1st 2 months, then 5 times/wk next 7 months + PE lessons + Total calorie intake 2300-2500 kcal/day.	9:0	HOMA-IR, and fasting glucose.
30	Pacifico 2013[58] Italy	Cohort: Total = 120	BMI > 95th %ile	Age range: 11.5-12.2 11.9 F=35%	Yes (method ND)	D+E: Clinic (Hospital)	Hypocaloric diet (25-30 cal/kg/day) + 60 min/day ~ 5 days/wk moderate exercise + Reduce sedentary behaviour.	12: 0	HOMA-IR, fasting glucose, CRP and ALT.
31	Panagiotopoulos 2011[59] Canada	Cohort: Total=119	Ob: BMI ≥ 95th %ile OW: BMI ≥ 85th %ile and <95th %ile with at least 1 comorbidity	Age range: 6-17. 11.6 ± 2.6. F=43%	NR	D+E: Clinic (Hospital)	10 x consecutive weekly group sessions (6-10 families): 30 min PA + nutrition session + behavioural session.	2.5: 0	HOMA-IR.
32	Parillo 2012[60] Italy	RCT: total=22	BMI z-score >2	Age range: HGI diet: 8.1- 12.5 LGI diet: 7.7- 13.0. HGI diet: 9.8 ± 1.6 LGI diet: 9.5 ± 1.6. F=53.8%	NR	D: Clinic (Hospital)	6 months: Participants randomised to a hypocaloric LGI or HGI diet (matched for macronutrient composition).	7: 0	HOMA-IR, fasting glucose and CRP.
33	Racil 2013[61] Tunisia	RCT : Total = 34 HIT=11 MIIT =11 OC=12	BMI > 97th %ile (French standards)	Age range: NR HIIT: 15.6 ± 0.7 MIIT: 16.3 ± 0.52 F=100%	Yes -Tanner	D+E: Community	4-day diet records + HIIT or MIIT. Interval training program 3 x /wk on non-consecutive days.	3: 0	HOMA-IR, and fasting glucose.
34	Racil 2016[62] Tunisia	RCT: Total = 47 HIIT =17 MIIT16 OC =14	BMI > 97th %ile (French standards)	Age range: NR 14.2 ± 1.2 F=100%	NR	E: AI	HIIT (Warm up + Interval training at 100%/50% MAS + Cooling down); MIIT (Warm up + Interval training 80%/50% MAS + Cooling down)	3: 0	HOMA-IR, and fasting glucose.

35	Rambhojan 2015[63] Guadeloupe	Cohort: Total=37	BMI z-score>2	Age range: 11-15. 12.7 ± 1.1. F=59%	Yes-Tanner	D+E: Community	Nutritional/health risks sessions, 5 hrs/week PE/PA + parent participation.	12: 0	HOMA-IR, and fasting glucose.
36	Reinehr 2004a[64] Germany OBELDICKS	Cohort: Total = 42	BMI ≥ 97th %ile	Age range: 6.1-15.1 10.2 F=57%	Yes - Tanner	D+E: Clinic (Hospital)	Obeldicks - Intensive phase 3 mnths (Parents' course 2x/month + Behaviour therapy 2x/month + Nutritional course 2x/month + Exercise therapy 1x/wk) + Establishing phase 3 mnths (Talk rounds for parents 1x/month + Psychological therapy + Exercise therapy 1x/wk) + Establishing phase 2 for 3 mnths (Psychological therapy + Exercise therapy 1x/wk) + Establishing phase 3 for 3 mnths (Exercise therapy 1x/wk).	12: 0	HOMA-IR, and fasting glucose.
37	Reinehr, 2004b[65] Germany	Cohort: Total=57	BMI ≥ 97th %ile	Age range: 6-14 (median: 10 years). F=54%	Yes-Tanner	D+E: Clinic (Hospital)	Obeldicks	12: 0	Fasting glucose.
38	Reinehr 2004c[66] Germany	Cohort: Total=130	BMI ≥ 97th %ile	Age range: 4-15. 10.7. F=53%.	NR	D+E: Clinic (Hospital)	Obeldicks	12: 0	HOMA-IR
39	Reinehr 2006[67] Germany	Cohort Total=203 (171 completers)	BMI ≥ 97th %ile	Age range: 6-14. 10.4. F=46.7%	NR	D+E: Clinic (Hospital)	Obeldicks	12: 0	HOMA-IR, and fasting glucose.
40	Reinehr 2008a[68], & 2008b[69] Germany OBELDICKS	Cohort: Total = 43 (plus n=19 lean)	IOTF using pop. -specific data	Age: Obese: 10.8 ± 2.6; F=61% Lean C: 10.3±2.9 F=58% (p<0.873)	Yes -Tanner	D+E: Clinic (Hospital)	Obeldicks	12: 0	HOMA-IR, fasting glucose, and ALT.
41	Reinher 2009a[70]	Cohort: Total=160 (152 completers)	IOTF using pop. -speficic data	Age range: 6-16. NR. Intervention F=47%. No intervention F= 40%	NR	D+E: Clinic (Hospital)	Obeldicks	12: 12	ALT
42	Reinehr 2009b[71] Germany	Cohort: Total=288	IOTF using pop. -speficic data	Age range: 10 to 16. mean 12.5. median 13.3. IQR 11.3-13.5. F=55%	Yes-Tanner	D+E: Clinic (Hospital)	Obeldicks	52: 0	Fasting glucose.
43	Reinehr 2015[72] Germany	Cohort: Total=40	IOTF using pop. -speficic data	Age range: 6-16. NR. F=50%	Yes-Tanner	D+E: Clinic (Hospital)	Obeldicks	12: 0	HOMA-IR, and fasting glucose.
44	Rijks 2015[73] Netherlands	Non-randomised prospective study Total = 145	IOTF criteria: Ow, Ob, MO	Ages: Ob: 2.6 - 18.9 Morb. ob: 4.1 - 18.9 Ob: 11.4 ± 3.2 Morb. ob: 12.3 ± 3.4 Ob: F=57 % Morb. ob: F=53%	NR	D+E: Clinic (Hospital)	Guidance with focus on nutrition, food habits, PA, sleep, psychological and social aspects.	24: 0	Fasting glucose and CRP.
45	Rohrer 2008[74] Germany Fit Kids	Cohort: Total = 22	BMI > 99.5th %ile (German standard values) or BMI > 97th %ile with obesity-	7-15. Median: 11.9 F=27%	NR	D+E: Community	Physical exercise (2 x wk, 100 hrs in total) + Nutritional/heath education and psychological care for the child (x wk, 43.5 hrs total) and parent/s (2 x wk, 12 hrs total).	12: 0	HOMA-IR and ALT.

			associated risk factors or BMI >90th %ile with obesity-associated disease						
46	Roth 2011[75]	Cohort: total=62	>97th Centile	Age range: NR. no sig weight loss 11 ±0.4 years. Weight loss 11 ±0.5 years. F=54%.	% prepubertal	D+E. Community.	Obledicks	12: 0	HOMA-IR, and fasting glucose.
47	Roth 2017[76] Germany OBELDICKS	Cohort: Total = 69	Ob as per IOTF criteria	NR - Obeldicks age range Ob with wt loss: 11.8 ± 2.0 F=50% Ob without wt loss: 12.1 ± 2.1 F=51% Normal wt: 12.3 ± 3.0 F=45%	Yes - Tanner	D+E: Clinic (Hospital)	Obeldicks	12: 0	HOMA-IR, fasting glucose, and ALT.
48	Rovira 2013[77] Spain	Cohort: Total=110. (88 completed)	BMI ≥ 97th %ile	Age range: 9-14. 12.1 ± 1.7. F=56%.	Yes- Tanner.	D+E: Clinic (Hospital)	12 x monthly visits in 2 phases: motivational and intervention. Focus on promoting healthy eating, encouraging PA & decreasing sedentary behaviour.	12: 0	HOMA-IR, and fasting glucose.
49	Santomauro 2011 [78] Venezuela	Cohort: Total=36	BMI > 97th %ile (according to Fundacredesa tables)	Age range: 7-18. 10.59 ± 2.96. F=42%	Yes-Tanner	D+E: Clinic (Hospital)	Dietary recommendations + 30 mins daily moderate exercise or 3 x week moderate exercise + decrease time watching TV/video games.	12: 0	HOMA-IR, fasting glucose, CRP, and ALT.
50	Savoye 2007[79], 2011[80] USA Bright Bodies	RCT + Long term FU results (cohort) Total = 174 I (BB)=105 Clinic C=69 FU Total = 159 (n=143 analysed)	BMI ≥ 95th %ile (CDC)	Age: 8-16 BB: 12.0 ± 2.5 F=55% Cl: 12.5 ± 2.3 F=68% NR 13.9 ± 2.4 F=62%	NR	D+E, I delivery: AI (local school). Measurements: Clinic (Hospital)	Bright Bodies (BB) Weight Management Program: nutrition education, exercise, behavioural modification. 2 x sessions/wk for 6 mths, then biweekly for next 6 mths. BB: 2x50 min exercise + 1x40 min nutrition/behaviour modification per wk + 12 mths no active intervention. Control group: std care – paed. obesity clinic (biannual clinic appt; diet + exercise counselling) Structured tx & teaching program (28 x 45 min therapeutic sessions e.g. PA, nutrition, healthy cooking)	12: 12 FU 1.5: 24	HOMA-IR, and fasting glucose.
51	Savoye 2014[81] USA, Bright Bodies.	RCT Total = 75 BB=38 CC =37	BMI ≥ 95th %ile	Age range: 10-16 BB – 12.7 (1.9) F=68% CC-13.2 (1.8) F=62%	Yes- Tanner	D+E: Academic Institution	BB weight management program- 2days/ week 30 min exercise sessions + 1 day/week 45 min nutrition.	6:0	HOMA-IR, fasting glucose and ALT.
52	Schum 2012[82] Germany	Cohort: Total = 25 (n=10 SMP, n=23 BFC)	BMI ≥ 95th %ile	Age range:11-16 13.5 ± 0.3 F=68%	NR	D+E: Clinic (Hospital)	BB Weight Management Program - 2 days/week 30 min exercise sessions + 1 day/week 45 min nutrition or BM group session	12: Monthly maintenance -	HOMA-IR.

								no explicit length	
53	Seabra 2016[83] Portugal	Cohort: Total = 88 soccer =29, Trad. Activity =29, OC =30	BMI-SDS > 2	8-12 Soccer: 10.5 ± 1.5 Trad. activity: 11.0 ± 1.6 F=0%	Yes - Tanner	E: Community	Soccer & trad. activity programmes (3 x 60-90min/wk) + 2 x 1hr at BL & 3 mnths later energy balance session.	6: 0	HOMA-IR, fasting glucose, and CRP.
54	Shalitin 2009[84] Israel	Cohort: Total = 174 randomised E =52 D =55 D+E = 55	BMI > 95th %ile for age & gender	6-11 NR F=50%	Yes - Tanner	D+E: Clinic (Hospital)	D +E 3-month interventions: Exercise intervention (90 min moderate exercise 3 days/wk); Diet intervention 3 mths (12 x/wk nutritional group meetings with parents + Hypocaloric diet 1200 kcal/day); Diet and exercise intervention 3 mths (90 min training session days/wk + 12 x/wk nutritional group meetings with parents + Hypocaloric diet 1200 kcal/day).	3 x 3 month :9	HOMA-IR,, fasting glucose, CRP, and IL-6.
55	Springer 2015[85] Germany	Cohort: Total=39	BMI > 90th %ile	Boys: 13.2-14.5 Mean=13.8 Girls: 13.6-14.6 Mean= 14.1 F=46%	Yes -Tanner	D+E: Clinic (Hospital)	Encouraged to increase exercise by 1-2 hrs/day + Decrease sedentary behaviour to a total of 2 hrs/day or less + Nutrition recommendations + 6 telephone calls from/visits to the physician.	7: 0	HOMA-IR and ALT
56	Truby 2016[86] Australia	RCT: Total = 87 SMC =37, SLF=36 WL OC =14	BMI > 90th %ile (CDC)	10-17 modified CHO diet: 13.2 ± 1.9 F=73% Low fat diet: 13.2 ± 2.1 F=72% Control: 13.6 ±1.9 F=71%	Yes- Tanner	D: Clinic (Hospital)	Structured modified CHO diet (35% CHO; 30% protein; 35% fat), structured low-fat diet (55% CHO; 20% protein; 25% fat), Control (no dietary advice).	3: 0	HOMA-IR, CRP, IL-6 and ALT.
57	Uysal 2014[87] Germany	Cohort: Total: 1017. n=484 intervention, n=533 obese control	BMI-SDS (Cole's LMS method with German population ref. data)	Age range: Intervention: 9.0-13 (IQR) Obese control: 10.3-14.1 (IQR). F=57%.	Yes- Tanner	D+E: Clinic (Hospital)	Intensive phase 3 months (Parent course 2x/month + Behaviour therapy 2x/mnth + Nutritional course 2x/mnth + Exercise therapy 1x/wk) + Establishing phase 3 mnths (Talk for parents 1x/mnth + Psychological therapy + Exercise therapy 1x/wk) + Establishing phase 2 next 3 mnths (Psychological therapy + Exercise therapy 1x/wk) + Accompanying families back to their everyday lives (Exercise therapy 1x/wk).	12:0	HOMA-IR and fasting glucose.
58	Valle Jiminez 2013[88] Spain	Cohort: Total=50	BMI >95th%ile growth curves for the Spanish population	Age range: 6.0-9.0. 8.02±0.15. f=58%	Yes- Tanner	D+E: Clinic (Hospital)	Behavioural components, physical exercise and nutritional education. Energy distribution of diet: 25% between breakfast & lunch; 30-35% at lunch; 15% afternoon snack; remainder dinner. Moderate-to-intense PA for 30 mins at least 3 days per wk. Aim that 1 month after the start of tx subjects should be engaging in 60 mins/day moderate-to-intense physical exercise.	9:0	HOMA-IR, and fasting glucose.

59	Van Hoorenbeck 2013[89] Belgium	Cohort: Total=224 (197 analysed)	ND. BMI Z score (based on Flemish growth charts) baseline: ODI<= 2.72 ±0.42 ODI≥2 = 2.78±0.41	Age range: ODI < 2: 10.2-18.0 ODI ≥ 2: 10.1-18.0. ODI < 2: 15.4 ODI ≥ 2: 15.9 ODI<2:F=74%. ODI ≥2 F= 48%.	NR	D+E: Clinic (Hospital).	Moderate dietary restriction (1400-1600 kcal/day) + Min 10 hrs/wk physical exercise + Psychological individual/group support and medical supervision.	4-6: 0	HOMA-IR, and ALT.
60	Van der Baan-Slootweg 2014[90] Netherlands	RCT: Total = 90 Inpt. = 45 (37) AmO = 45 (36)	BMI z score ≥ 3.0 or > 2.3 with obesity-related health problems	Age range: 8-18 Inpt: 13.8 ± 2.3; F=58% AmO: 13.9 ± 2.5; F=58%	NR	D+E: Clinic (Hospital)	Inpt. (Hospitalised 26 wks on working days - 4 days/wk 30-60min exercise + nutrition/BM once/wk + parents/caregivers 3 x 1hr lesson on nutrition/BM); Ambulatory (12 visits at increasing time intervals - 1 hr exercise session + encouraged 3 x exercise/wk + 1 hr educational programme + 30 min nutrition education).	6: 24	HOMA-IR, fasting glucose and ALT
61	Verduci 2011[91] & Pozzato 2010[92], Italy.	RCT: total= 26	BMI Cole's curve cut-off 30 kg/m^2 or cut-off 18.5-25 kg/m^2 at 18 yrs	Age range: 6 to 14. NR. F=58%.	Yes-Tanner	D+E: Clinic (Hospital) + Community	Normocaloric balanced diet + 1 hr nutritional counselling + Encouraged 30-45 min/day aerobic physical exercise.	12: 0	HOMA-IR, and fasting glucose.
62	Verduci 2015[93] Italy	RCT: Total = 90 Inpt. = 45 ambulatory = 45	BMI z score ≥ 3.0 or > 2.3 with obesity-related health problems	8-18 Inpt: 13.8 ± 2.3 F=58% Ambulatory: 13.9 ± 2.5 F=58%	NR	D+E: Clinic (Hospital)	Inpt. (Hospitalised 26 wks on working days - 4 days/wk 30-60min exercise + nutrition/BM once/wk + parents/caregivers 3 x 1hr lesson on nutrition/BM); Ambulatory (12 visits at increasing time intervals - 1 hr exercise session + encouraged 3 x exercise/wk + 1 hr educational programme + 30 min nutrition education).	6: 24	HOMA-IR, and fasting glucose.
63	Visuthranukul 2015[94], Thailand	RCT: Total = 70 randomised. I = 25 OC=27 analysed	ND. BL BMI z-score: I = 3.7 ±0.9 C = 3.6±1.6	9-16 I = 11.9 ± 1.9 F=36% C = 12.0 ± 2.1 F=30%	Yes- Tanner	D: Clinic (Hospital)	I (Low GI diet + Energy restriction 1400-1500 kcal/day + Increased exercise); OC (Energy restriction 1200-1300 kcal/day + Low fat/high fibre diet + Increased exercise).	6: 0	HOMA-IR, fasting glucose and ALT.
64	Vitola 2009[95], USA	Cohort: Total = 8	BMI ≥ 95th %ile	Age range: NR 15.3± 0.6 F=12.8%	Yes- Tanner	D+E: Clinic (Hospital)	Behavioural goals for reducing calorie intake and gradually increasing PA. calories around 1200-1500 Kcal.	No specific time frame	HOMA-IR, fasting glucose and ALT.
65	Vos 2011[96], Netherlands	RCT Total =79 I=40 OC=39	Cole et al criteria	Age range: 8-17 I: 13.3 ± 2 C: 13.1 ± 1.9 F=55%	Yes - Tanner	D+E: Clinic (Hospital)	12 mnths: During first 3 mnths (7 x 2.5 hr/2 wks children group meetings + 5 x 2.5 hr/2 wks parent meetings + 1 x 2.5 hr/2 wks child/parent meeting + 2-3 refresher follow-up sessions for total of 2 yrs). CG received std care + advice.	3: 9	HOMA-IR, fasting glucose and CRP.
66	Weiss 2009[97] USA	Cohort: Total=186	BMI > 95th %ile (CDC)	Age range: 6-18. 13.1 ± 2.5. F=57%.	NR	D+E. Clinic (Hospital).	Subjects followed biannually as outpatients + Received nutritional/PA guidance. Levels of adherence to these recommendations was not evaluated or documented	24: 0	Fasting glucose.

67	Wickham, 2009[98] & Evans 2009 [99] USA TEENS (same cohort)	Cohort: Total = 168 (64) *	BMI ≥ 95th %ile (CDC)	Age range: 11-18 13.4 ± 1.8; F=60% 13.9 ± 1.9; F=62%	NR	D+E: Academic Institution	E 1 day/wk at facility + 2 additional E days at facility of ppts' choice + 30 min/wk nutrition education/behavioural support sessions.	6: 0	HOMA-IR and fasting glucose.
68	Wunsch 2006 [100] Germany	Cohort: Total=56.	BMI > 97th %ile	Age range: 8.3-9.1. 8.7. F=66%.	NR	D+E: Clinic (Hospital)	Obeldicks	12: 0	HOMA-IR, and fasting glucose

KEY: %ile = percentile; AmO = Outpatient Ambulatory; An. = analysed; apt. = Appointment; BB =Bright Bodies; BFC = Better food choices; BL = baseline; BM = behaviour modification; BMI= body mass index; C = control; CG: control group; CBT = cognitive behavioural therapy; CDC = Centre for Disease Control; CG = control group; CHO = carbohydrate; D = diet; E = exercise; FBBT = family-based behavioural treatment; F = female; FU = follow up; GI = glycaemic index; GT = group therapy; HGI = high glycaemic index; hr = hour; ht = height; I = intervention; IG= intervention group; IOTF = International Obesity Task Force; Inpt. = inpatient; LGI = low glycaemic index; LMS= least-mean-squares; LS = long stay; min= minute; mth = month; MO = morbidly obese; norm. normal; n = number; NAFLD = Non-alcoholic fatty liver disease; ND = not described; NR = not reported; OB = obese; OC = obese control; OW = overweight; paed. = paediatric; PA = physical activity; PE = physical activity; PROT= protein; RCT = randomised controlled trial; SD = standard deviation; SDS = standard deviation score; SMP= Structured meal plan; SS= short stay; SMC= structured modified carbohydrate diet; trad. = traditional; Trad. act = traditional activity; tx = treatment; wk = week; WList OC– wait list obese control; WL = weight loss; wt = weight; X-over = crossover; yr = year CRP=C-reactive protein; ALT=Alanine Aminotransferase; IL-6=Interleukin-6; HOMA-IR= Homeostatic model assessment insulin resistance, QUICKI= Quantitative Insulin Sensitivity Check Index

Legends

Figure 1 Flow diagram to show the search results and various stages of exclusion for the systematic review.

Table 1: Characteristics of studies reporting adiposity outcomes

Figure 2: Meta-regression of relationship between mean change in HOMA-IR and the mean change in BMI-SDS (n=105 subsets).

Figure 3: Meta-regression of relationship between mean change in fasting glucose and the mean change in BMI-SDS (n=92 subsets)

Figure 4: Meta-regression of relationship between mean change in ALT and the mean change in BMI-SDS (n=28 subsets)

Figure 5: Meta-regression of relationship between mean change in CRP and the mean change in BMI-SDS (n=36 subsets)

Appendix 2

Figure A(i) Half normal plot for the predicted random effects from the meta-regression of the mean change in HOMA-IR and the mean change in BMI SDS (n=105, see main text).

Figure A(ii) Meta-regression of relationship between mean change in HOMA-IR and the mean change in BMI-SDS.

Figure A(iii) Meta-regression of relationship between mean change in HOMA-IR and the mean change in BMI-SDS using only the 22 data subsets where the mean and SD of the changes are given in the paper.

Figure B(i) Half normal plot for the predicted random effects from the meta-regression of the mean change in fasting glucose and the mean change in BMI SDS (n=92, see main text).

Figure B(ii) Meta-regression of relationship between mean change in fasting glucose and the mean change in BMI-SDS after excluding two outliers (n=90, see main text).

Figure C(i) Half normal plot for the predicted random effects from the meta-regression of the mean change in ALT and the mean change in BMI SDS (n=28, see main text).

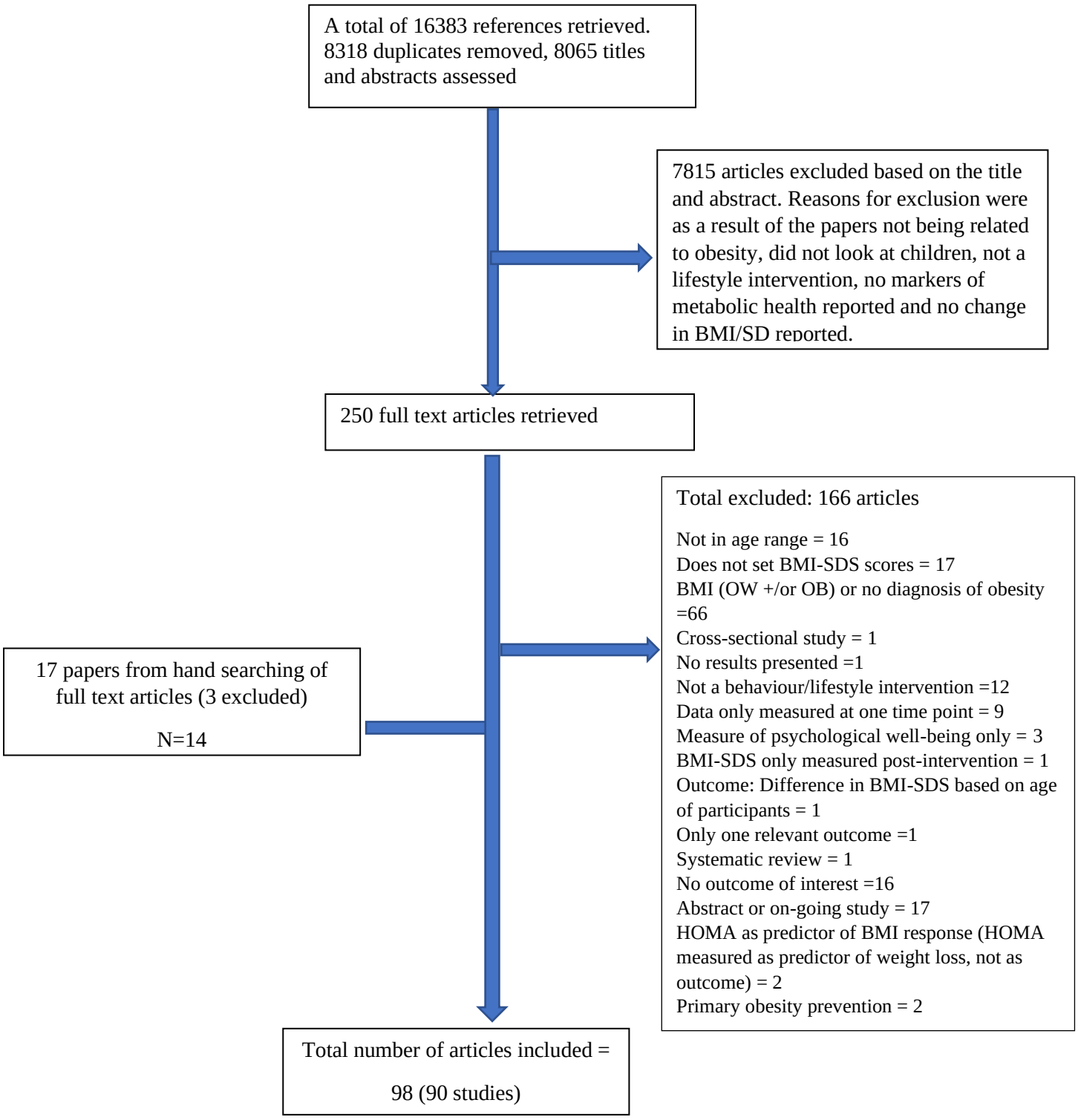
Figure D(i) Half normal plot for the predicted random effects from the meta-regression of the mean change in CRP and the mean change in BMI SDS (n=36, see main text).

Supplementary material

Figure 6: Venn diagram to show the different number of studies included in the three different papers.

Table 2: Quality Assessment of included studies

Figure 1. Flow diagram from the systematic review that identified the included studies



Appendix 2

Fig A(i) Half normal plot for the predicted random effects from the meta-regression of the mean change in HOMA-IR and the mean change in BMI SDS (n=105, see main text).

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Figure A(ii) Meta-regression of relationship between mean change in HOMA-IR and the mean change in BMI-SDS.

Figure A(ii) shows the meta-regression of Figure 2 in the main paper but highlights (in red) the 4 study subsets where geometric means were used interchangeable with medians. The results seemed consistent with the remainder and their exclusion did not change our overall findings (not shown).

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Figure A(iii) ***Meta-regression of relationship between mean change in HOMA-IR and the mean change in BMI-SDS using only the 22 data subsets where the mean and SD of the changes are given in the paper.***

The fitted regression line **was Mean fall in HDL = 1.498 x Mean change in BMISDS + 0.022.** From these limited data, we could not determine a mean change in BMI-SDS that would ensure a mean reduction of HOMA-IR; there was a weak relationship between these values that failed to reach statistical significance (P=0.058). The Adjusted R-squared was 21% and the I^2 was 87%.

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Fig B(i) Half normal plot for the predicted random effects from the meta-regression of the mean change in fasting glucose and the mean change in BMI SDS (n=92, see main text).

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Figure B(ii) ***Meta-regression of relationship between mean change in fasting glucose and the mean change in BMI-SDS after excluding two outliers (n=90, see main text).***

The meta-regression line fitted was: **Mean fall in Glucose = 0.075 x Mean change in BMISDS -0.006.** The small positive slope was not statistically significant (P=0.068). From the prediction intervals, it was not possible to determine a mean reduction in BMI Z-score that would ensure a fall in Glucose. The I^2 and adjusted R^2 were 83% and 3% respectively.

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Fig C(i) Half normal plot for the predicted random effects from the meta-regression of the mean change in ALT and the mean change in BMI SDS (n=28, see main text).

INSERT HERE

Fig D(i) Half normal plot for the predicted random effects from the meta-regression of the mean change in CRP and the mean change in BMI SDS (n=36, see main text).

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Appendix 1:

Eligibility criteria for inclusion to the systematic review

Participants

Studies with participants aged 4–19 years with a diagnosis of obesity using defined BMI thresholds were considered for inclusion. BMI-SDS was calculated as a function of the degree of obesity of the subjects when compared with BMI standards. BMI standards included, but were not limited to, the 98th centile on the UK 1990 growth reference chart[28], 95th percentile on the US Centre for Disease Control and Prevention growth chart[29], the International Obesity Taskforce (IOTF) BMI for age cut-points[30] and the World Health Organisation growth references [31,32], in addition to country-specific obesity thresholds using BMI reference data from their paediatric populations. Studies that included overweight, as opposed to obese, individuals, pregnant females, or those with a critical illness, endocrine disorders or syndromic obesity were excluded from this review.

Interventions

Studies of lifestyle treatment interventions that included dietary, physical activity and/or behavioural components with the objective of reducing obesity were included. Interventions of less than 2 weeks duration and those that involved surgical and/or pharmacological components (e.g. bariatric surgery, drug therapy) were excluded. Studies focused on obesity prevention were also excluded. No restrictions were imposed regarding the setting or delivery of the interventions.

Outcome measures

To meet the inclusion criteria interventions had to report baseline (pre-) and post-intervention BMI-SDS/z-score or change measurements of BMI-SDS/z-score plus one or more of the following markers of metabolic health:

- Adiposity measures other than BMI (including waist circumference and percentage body fat)
- Glucose
- Insulin sensitivity/resistance (homeostatic model assessment (HOMA))

- Lipid profile (triglycerides, total cholesterol, low-density lipoprotein (LDL)/high-density lipoprotein (HDL) cholesterol)
- Inflammation (C-reactive protein)
- Blood pressure (systolic, diastolic)
- Liver function

This paper focuses on the inflammation, diabetes and liver function measures only. Further papers in this series will report on other outcome measures.

Study design

Completed, published, randomised controlled trials (RCTs) and non-randomised studies (cohort studies) of lifestyle treatment interventions for obese children and adolescents, with or without follow-up.

Information sources and search methods

Studies were identified by searching five electronic databases from inception to May 2017, alongside scanning reference lists of included articles and through consultation with experts in the field.

Study Selection and data extraction

Titles and abstracts were assessed for eligibility and data were extracted by two independent reviewers from the review team (LB, AC, RP, RB, RM).